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NTP Technical Report on

Toxicity Studies of

N,N-Dimethylformamide

(CAS NO: 68-12-2)

Administered by Inhalation
to F344/N Rats and B6C3F$_1$ Mice

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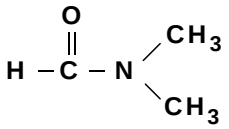
N,N-Dimethylformamide



Molecular Formula: C_3H_7NO

CAS Number: 68-12-2

Molecular Weight: 73.09

Synonyms: DMF, DMFA

ABSTRACT

N,N-Dimethylformamide (DMF), a colorless liquid with a high boiling point, is a solvent used in a large number of industrial processes. Male and female F344/N rats (30/sex/group) and $B6C3F_1$ mice (10/sex/group) were exposed to DMF vapors at concentrations of 0, 50, 100, 200, 400, or 800 ppm, 6 hours/day, 5 days/week, for 13 weeks in whole body exposure inhalation studies. In addition to histopathology, sperm morphology, and vaginal cytology, which were evaluated in both species, the studies examined clinical pathology, cardiovascular, and renal function in rats only.

In genetic toxicity studies, DMF was not mutagenic in *Salmonella typhimurium* strains TA100, TA1535, TA1537, or TA98, with or without S9 activation, nor did it induce germ cell mutations in male *Drosophila melanogaster* treated by feeding or injection. No induction of sister chromatid exchanges or chromosomal aberrations was noted in cultured Chinese hamster ovary cells treated *in vitro* with DMF, with or without an S9 metabolic activation system. In one laboratory, a marginal increase in mutant colonies was observed after treatment of mouse lymphoma $L5178Y/TK^{+/-}$ cells with DMF in the absence of S9; results from studies in 2 other laboratories were negative.

In the 13-week studies, all rats survived exposures to DMF. Body weight gains were reduced by 50-65% in rats exposed at 800 ppm and to a lesser extent in the 400 ppm group. Evidence of hepatocellular injury was noted as early as day 4, based on increases in activities of liver-specific enzymes in serum in rats of both sexes exposed at 200-800 ppm. Serum cholesterol levels were increased at all exposure concentrations. Relative liver weights were increased in male rats exposed at 100 ppm and higher concentrations, and in female rats at all concentrations. Minimal to moderate centrilobular hepatocellular necrosis was seen in rats of both sexes exposed at 400 and 800 ppm; the lesion was more severe in females.

There were no clear, adverse effects seen in urinalyses, in electrocardiographic studies, or in male reproductive system evaluations that could be related to DMF exposure. Hematologic studies showed mild hemoconcentration in males and females. Prolonged diestrus was observed in females exposed at 800 ppm.

Among mice exposed to DMF for 13 weeks, there was no chemically related mortality. Body weight gains were approximately 30% less than controls in females exposed at 800 ppm. Relative liver weights were increased in males and females at all exposure concentrations. Centrilobular hepatocellular hypertrophy (minimal to mild) was found in all groups of male mice exposed to DMF, and in female mice exposed at 100 ppm and higher concentrations. The length of the estrous cycle in mice increased with increasing DMF exposure.

In summary, DMF-related effects were seen in the liver of both rats and mice, with rats being more severely affected. For rats of both sexes, the no-observed-adverse-effect level (NOAEL) was 200 ppm, based on the absence of liver histopathology, although liver function assays and liver weights showed changes at all exposure levels (as low as 50 ppm). For mice, hepatocellular hypertrophy or increased liver weights occurred at all exposure concentrations.

PEER REVIEW

Peer Review Panel

The members of the Peer Review Panel who evaluated the draft report on the toxicity studies of N,N-Dimethylformamide on November 21, 1991, are listed below. Panel members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, panel members act to determine if the design and conditions of the NTP studies were appropriate and to ensure that the toxicity study report fully and clearly presents the experimental results and conclusions.

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Summary of Peer Review Comments

Mr. D. Lynch, NIOSH, introduced the draft report on the short-term toxicity studies of N,N-dimethylformamide (DMF) by reviewing the uses and rationale for study, experimental design, and results.

Mr. Beliczky, a principal reviewer, noted commented that the report was well-written. He noted that extra groups of rats were included for special studies of cardiovascular function and renal function as well as clinical pathology and asked why this was not done for mice. Mr. Lynch replied that the larger body size and base of experience for these studies in rats were the primary reasons for doing the studies in rats while cost was probably a reason for not doing the studies in mice. Mr. Beliczky asked whether the study had been initiated because of increased incidences of testicular cancers among aircraft maintenance workers and leather tanners. Mr. Lynch said that was certainly one rationale. Mr. Beliczky reported that he had heard that DuPont was conducting a 2-year bioassay and asked whether results were available. Mr. Lynch affirmed this and noted that the study was in rats; the in-life phase would be completed in December, 1991; and a report would be available in 1992.

Dr. Bailey, a second principal reviewer, said this was a good report, and the data presented supported the conclusions drawn. He commented that a recent report in the literature indicated that while the metabolite, AMCC (believed to be in the pathway leading to electrophilic products), was a minor metabolite in rodents it was of primary importance in humans. Thus, the risk of toxicity from exposure to DMF would appear to be higher in humans than in rodents. Mr. Lynch said he had not been aware of that reference and would add it.

Dr. Klaassen noted the increased serum cholesterol levels and wondered whether cholesterol was routinely measured. Dr. M. Thompson, NIEHS, said cholesterol wasn't routinely measured, but it seemed to be a fairly sensitive indicator of hepatocellular function, which in the current study would be consistent with the hepatotoxicity observed.

Seeing no objections, Dr. Klaassen accepted the report, with the suggested editorial and other changes, on behalf of the panel.